ETHICS

Incidental Findings in Brain Imaging Research

What should happen when a researcher sees a potential health problem in a brain scan from a research subject?

Judy Illes,[1,2] Matthew P. Kirschen,[1–3] Emmeline Edwards,[5] L R. Stanford,[6] Peter Bandettini,[7] Mildred K. Cho,[1,4] Paul J. Ford,[8] Gary H. Glover,[2] Jennifer Kulynych,[9] Ruth Macklin,[10] Daniel B. Michael,[11] Susan M. Wolf[12] and members of the Working Group on Incidental Findings in Brain Imaging Research[13]

Research imaging studies have provided a steady stream of fundamental knowledge about the relation between brain and behavior in health and disease. Recent reports of clinical findings detected incidentally in this research (*1*–*3*), however, have created interest in the implications and ethics of how these findings are handled. We define incidental findings as observations of potential clinical significance unexpectedly discovered in healthy subjects or in patients recruited to brain imaging research studies and unrelated to the purpose or variables of the study. We believe that all investigators engaged in brain imaging research should anticipate incidental findings in their experimental protocols and establish a pathway for handling them. The central issues for consideration are how to protect subject welfare and research integrity while appropriately addressing investigator responsibility, subject expectations, informed consent, professional training of the research team, and the financial cost of following up on incidental findings. Protecting human subjects is of paramount importance.

This article summarizes the views presented at a workshop sponsored by the U.S. National Institutes of Health (NIH) (*4*) and ongoing work, but it does not reflect endorsement by or an official position of the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Drug Abuse (NIDA), the National Institute of Mental Health (NIMH), NIH, or any other Federal agency. It is intended to advance discussion of the issues only (*5*). Any future official recommendations on incidental findings should promote trust in research without unduly encumbering the scientific process.

Published data indicate that clinically significant and identifiable neuropathologies occur in 0.5 to 2% of the population (*6*). There have been some reports of higher rates of incidental findings with varying degrees of clinical significance (*1*–*3*, *7*, *8*). Low rates of clinical disease have also been reported by the Central Brain Tumor Registry of the United States (*9*). Taken together, these data raise the possibility of a high rate of false-positives in incidental findings.

"Any future official recommendations on incidental findings should promote trust in research without unduly encumbering the scientific process."

Issues concerning communication focus on whether incidental findings in research should be disclosed to subjects at all and, if so, what are the obligations of researchers to communicate them, when, and to whom. The discussion is made especially complex by the absence of professional guidelines and the current landscape of imaging investigators that includes undergraduate and graduate students, fellows, and M.D. and Ph.D. investigators. A practical obstacle in establishing guidelines is that there are no data on the usefulness of brain imaging as a screening tool in asymptomatic individuals, particularly the typically lower-resolution and contrast magnetic resonance (MR) images collected for research.

The majority of the working group (*10*) felt that a research protocol that provides for disclosure of suspicious incidental findings to subjects is ethically desirable. This view is based on researcher obligations to respect subjects' autonomy and interests, demonstrating reciprocity when subjects agree to participate in studies by communicating a finding that may have a health impact (*11*). This view is also informed, in part, by results of a recent study (*12*) in which subjects who had previously participated in brain imaging studies were queried for their expectations about incidental findings. Whether scanned at an imaging facility affiliated with a medical center or at a nonmedical site associated with a university psychology department, subjects reported that they expected an abnormality to be detected if present. An average of 97% reported that they wanted a finding to be disclosed to them regardless of its potential clinical significance. Much remains to be learned about the source of subjects' expectations in such studies, including their understanding of informed consent.

The potentially harmful consequences of false-positive reports on normal volunteers have not been explored. Some members of the working group felt that the potential of false-positives rendered it unwise to communicate all but the most certain incidental finding.

Wide variability exists in both when and how incidental findings are handled for the estimated tens of thousands of human subjects involved in imaging research per year. In one survey of MR imaging laboratories, 36% reported that all their research scans are read by a neuroradiologist and findings disclosed, 47% only when a suspicious finding is detected, 4% depending on type of study, and 13% not at all (*2*). Some research centers are not associated with clinical facilities, and anomalies may be detected by and reported to the subject by nonphysicians. In these cases, the subjects are informed that the scan is a research scan, that the researchers are nonphysicians, and that they are not qualified to evaluate any anomalies detected. Data of potential medical significance may be made available to a physician if the subject chooses, but should never be disclosed without explicit authorization of the subject or a surrogate when the subject is a minor or an adult without decisional capacity.

Vulnerable populations and subjects without a primary-care physician or without medical insurance may need extra assistance in

[1]Center for Biomedical Ethics, [2]Department of Radiology, [3]Program in Neuroscience, [4]Department of Pediatrics, Stanford University, Palo Alto, CA 94304, USA. [5]National Institute of Neurological Disorders and Stroke, [6]National Institute on Drug Abuse, [7]National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892, USA. [8]Department of Bioethics, Cleveland Clinic Foundation, Cleveland, OH 44195, USA. [9]Legal Department, Johns Hopkins Hospital and Health System, Washington, DC 20005, USA. [10]Department of Bioethics, Albert Einstein College of Medicine, Bronx, NY 10461, USA. [11]Michigan Head and Spine Institute, Southfield, MI 48075, USA. [12]Law School, Medical School, and Center for Bioethics, University of Minnesota, Minneapolis, MN 55455, USA. [13] Names and affiliations are provided in the Supporting Online Material.

*Author for correspondence. E-mail: illes@stanford.edu

identifying avenues for follow-up consultation. A minority of the group felt it was not ethical to leave all of the responsibility for follow-up to the subject. They made the points that research scans are typically not of the quality needed to make a clinical assessment and, second, obtaining a clinical scan is very expensive and can jeopardize future medical insurability.

One of the greatest sources of discussion among the group was whether or not a physician competent to read scans should be part of all research imaging studies when the principal investigator does not have those qualifications or is not trained as a medical doctor. The majority of the working group maintained that when a research protocol provides for communicating an incidental finding, the principal investigator is obligated to have the presence of a finding validated by a physician competent to read the scan. However, researchers in nonmedical settings may not have access to physician support.

Furthermore, communication itself is an issue when the principal investigator is not a physician trained to communicate medically sensitive information. This makes a single approach to the communication question elusive and should be the subject of further discussion and study.

Well-recognized ethics arguments in the medical screening (*13*) and genetics literature (*14*), for example, support a subject's right not to know. Investigators have an obligation to provide this option to subjects in the consent process. The subject opt-out option does expose investigators to a significant ethical conundrum, however, in the event of a clearly identified, life-threatening, treatable lesion. In that case, respecting subject autonomy is difficult to reconcile with a Good Samaritan ethos.

Although it is the investigator's choice to determine the scans necessary to meet the scientific goals of a study, it is the Institutional Review Board's (IRB's) responsibility to ensure that pathways for handling incidental findings in studies are explicit in the research protocol and in the written and verbal informed consent process. Investigator training should address explicit procedures for managing incidental findings. The pathway should address who will evaluate a suspected incidental finding and to whom the finding will be communicated. Statistics about the incidence of unexpected findings and the proportion with potential clinical significance may fruitfully be offered in the consent process; the sources of the data should be cited.

Investigators may worry that asking a physician to verify the presence of a suspicious incidental finding will compromise the subject's privacy. Researchers may seek consent for such communication in the process of obtaining the subject's consent to participating in the research. Alternatively, the researcher may de-identify the data before transmission. However, communication even with identifiers may well be allowed under state and federal privacy law because it is for the purpose of potential treatment. IRBs should recognize that some principal investigators might elect to opt out of evaluating incidental findings at all. This choice should be communicated to the IRB in protocols submitted for review and to research subjects during the process of obtaining informed consent.

Concerns about the sheer numbers of scans and the cost burden of routine readings were central to participants both affiliated with and not affiliated with medical centers. The group discussed how costs could be mitigated by discounts for research, for scan volume, or by written acknowledgment. Academic acknowledgment, as in publication, may be appropriate if a physician is a full member of the research team.

We saw no ethical requirement to acquire additional screening or clinical scans beyond those required for the research. Although we noted that intramural researchers at the NIH Clinical Center and investigators at some other institutions may obtain a clinical scan screened by a neuroradiologist for each subject in an imaging study, the majority of our group felt that requiring a clinical screening for each participant would be overly costly and impractical considering the unknown incidence of true-positive, clinically significant incidental findings in asymptomatic individuals. This is a consideration particularly for the growing number of research settings in which imaging studies are not performed within medical centers.

Our work lays the foundation for handling incidental findings in brain imaging, but further research is needed to evaluate the costs and benefits of identifying incidental findings and referring subjects for follow-up. How the burden of false-positives, combined with the burden of testing for incidental findings, weighs against the problem of missed incidental findings must be assessed. We must understand the downstream financial cost on the investigative process, and the psychological and financial burden that discovery of an incidental finding might have on subjects, in parallel with thinking about incidental findings upstream. The impact of an unexpected finding on a parent when a child is concerned, for example, is a particularly compelling problem. To this end, determining the frequency of confirmed and false-positive findings and developing age-appropriate and even disease-specific databases is imperative.

Beyond the points discussed here, we also concluded that it is premature to attempt to identify incidental findings in imaging data about brain function. This is the case whether the nonmorphologic brain data are obtained from MR or other types of functional imaging. We recommend, however, that researchers remain aware of the issues surrounding incidental findings as single-subject functional data become better understood.

Other ethical challenges surfaced during the course of our work. These included, for example, responsibility and management of findings that occur in secondary data analysis through shared databases. Additional issues, such as those that may arise for third parties upon a finding suggestive of heritable disease, were also raised for future analysis.

Our recommendations, like our disagreements, were guided by our commitment to scientific and ethical responsibility. Legal considerations are important, but they did not drive this effort. Our desire is to be proactive in order to ensure scientific integrity and to engender public trust. Even while future research on this topic evolves, investigators must have a method in hand for grounding their reasoning and choices for handling incidental findings.

References and Notes

1. J. Illes, J. E. Desmond, L. F. Huang, T. A. Raffin, S. W. Atlas, *Brain Cogn.* **50**, 358 (2002).
2. J. Illes *et al.*, *J. Magn. Reson. Imaging* **20**, 743 (2004).
3. G. L. Katzman, A. P. Dagher, N. J. Patronas, *JAMA* **282**, 36 (1999).
4. "Detection and disclosure of incidental findings in neuroimaging research," workshop, Bethesda, MD, 6 to 7 January 2005 (NIH and Stanford University); (www.ninds.nih.gov/news_and_events/proceedings/ifexecsummary.htm).
5. To participate in an online discussion on incidental findings, go to http://neuroethics.stanford.edu and click on "Incidental Findings—Open Discussion Forum."
6. F. Weber, H. Knopf, *J. Neurol. Sci.* **240**, 81 (2006).
7. J. Illes *et al.*, *Neurology* **62**, 888 (2004).
8. B. S. Kim, J. Illes, R. T. Kaplan, A. Reiss, S. W. Atlas, *Am. J. Neuroradiol.* **23**, 1674 (2002).
9. Central Brain Tumor Registry of the United States, 2004–2005 Statistical Report: "Primary brain tumors in the United States, 1997–2001" (www.cbtrus.org).
10. About 50 experts in imaging, biomedical ethics, policy, law, and other relevant fields met (*4*). The term "majority" is used to indicate when a view emerged from the discussion that the leaders and participants felt was the predominant view expressed. All coauthors and workshop participants were able to interact and contribute to writing this paper at a password-restricted Web site. Coauthors from the working group are identified in the supporting online material.
11. D. I. Shalowitz, F. G. Miller, *JAMA* **6**,737 (2005).
12. M. P. Kirschen, A. Jaworska, J. Illes, *J. Magn. Reson. Imaging*, published online 13 January 2006 (doi: 10.1002/jmri.20499).
13. K. A. Quaid, *Am. J. Cardiol.* **72**, 64D (1993).
14. E. W. Clayton, in *Genetic Secrets: Protecting Privacy and Confidentiality in the Genetic Era*, M. A. Rothstein, Ed. (Yale Univ. Press, New Haven, CT, 1997), pp. 126–136.

15. The workshop (*4*) was supported by NINDS, NIDA, National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institute on Aging (NIA), NIMH, and NINDS grant R01 NS045831 (J.I.). Support for early work on incidental findings from the Greenwall Foundation is also gratefully acknowledged.

10.1126/science.1115429

Supporting Online Material
www.sciencemag.org/cgi/content/full/311/5762/783/DC1